REMARKS

I. Status of Claims

Claims 1- 4, 6-43, 45,47-49 and 51 are cancelled.

Claims 5, 44, 46 and 50 are amended.

Claims 5, 44, 46 and 50 are being prosecuted.

II. Interview Summary

Participants on March 24, 2009, in a telephonic interview were:

Dr. Byron Anderson (Inventor)
Alice Martin and Richard Lazarus (Applicant's Representatives)
Doug Schultz and Christopher M. Gross (USPTO)

Dr. Anderson explained that the limitation "at least 68% of the D-peptides consist of at least three 3 aromatic D-amino acid residues" was inherent in the libraries of the peptides claimed, not just in the pentapeptides. The protocol for making these peptide combinatorial libraries, by what is termed a split synthesis method, results in percents of peptides with certain characteristics that are intrinsic to the method and the amino acids used to construct the libraries. The inventor had previously explained this to the examiner, and the examiner already agreed in the record that the limitation applied to pentapeptides, but questioned whether the limitation applied to peptides of other lengths.

Dr. Anderson promised a demonstration of the meaning of "at least 68%" for 3, 4, 6, 7-mer peptides as he had for the pentapeptides, which the examiner accepted in the record.

Also, there appeared to be an disagreement about interpretation of the phrase "linked D-peptides are soluble relative to surrounding...."

Dr. Anderson explained the meaning with regard to a peptide library and its function.

III. Withdrawn Rejections

Applicant thanks the examiner for removing 35 U.S.C. 103(a) rejections over various combinations of Momany, Barany et al. and Dooley.

IV. "At least 68%" is Supported for all Peptide Lengths of 3 to 7 amino acids[1]

The protocol for making the peptide combinatorial libraries is described in the specification [0018] and [0049], is accomplished using a split synthesis method that has been described in the literature, and results in each bead containing multiple copies of one peptide sequence. The bead mixtures, after completion of a desired library, consist of all possible combinations of the amino acid residues constituting the library. These amino acids were specified as D-phenylalanine, D-tyrosine, D-tryptophan, D-alanine and/or glycine. The specification relates that the key feature of peptides binding to various proteins with high affinities was the presence of 3 or more aromatic residues{[0075] "of the total sequences obtained, 90% contain three or four aromatic D-amino acids. Of those sequences identified from the G and A sublibraries (i.e., D-peptides with glycine or D-alanine residues at the amino-terminus), 89% contained three or four aromatic D-amino acids."; and in [0081] describing peptides binding to TNFalpha and TGFbeta, "Two of the 27 total sequences (7%) contained two aromatic D-amino acids; six (22%) contained three aromatic D-amino acids; 17 (63%) contained four aromatic D-amino acids; and two (7%) contained five aromatic D-amino acids."]. In this latter case the peptides containing 3 or more aromatic D-amino acids adds up to 95%. Thus it is quite clear that one of the key findings of the specification is that those peptide sequences binding with high affinities to proteins of interest are those containing 3 or more aromatic D-amino acids.

As related in a prior response and in the most recent interview with the examiner, the percents of peptides in the libraries containing 3 or more aromatic amino acid residues is intrinsic to the way the libraries are made; the percent values cannot be anything else. The examiner already agreed in the record that this limitation applied to the pentapeptide library – the same principle necessarily applies to all such libraries.

Dr. Anderson repeats here[2] the calculations of percents of peptides in the pentapeptide library that contain 3 or more aromatic D-amino acids, and as promised in the interview, includes the demonstrations that the tri-, tetra- hexa- and hepta-peptide libraries all consist of at least 68% of sequences containing 3 or more aromatic D-amino acids, as the examiner had accepted for the pentapeptide library. The calculations of these percents requires only simple logic and simple math.

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1 Citations are to US 2004 0147716.

2 If required, Dr. Anderson's comments will be submitted in a Declaration.

The examiner acknowledged that the limitation as applied to pentapeptides was supported. The percents of peptides containing 3 or more aromatic amino acids in all libraries is intrinsic to the synthetic method used to synthesize the libraries (the split synthesis method). These percents cannot be anything other than what they are. One can specify any of the possible combinations of types of amino acids in any of the libraries and then calculate their percent of all sequences. Three or more aromatic D-amino acid residues in a peptide was key to those peptides that bound to proteins of interest with high affinities, as expressed in claim 5.

As promised in the Interview, calculations are presented in support of the limitation of "at least 68%" of the peptides consist of at least three aromatic D-amino acid residues. The specification describes the split synthesis method. The percents of peptides that would contain 2, or 3, or 4 aromatic amino acid residues are in the specification, [0016]: "About 23% of the pentapeptides in the library made by the split synthesis method contain two aromatic D-amino acid residues, about 34% contain three aromatic D-amino acid residues, and about 25% contain four aromatic D-amino acid residue." Adding the percent of peptides that contain 5 aromatic D-amino acid residues in the pentapeptide library, the percent of 3 or more such residues is 68%.

Pentapeptide Combinatorial Library:

In order to do the calculations, one first determines the number of "permutations" in a peptide that contain 3 or more aromatic residues (which will mean D-phenylalanine, D-tyrosine and D-tryptophan). For example, in the pentapeptide, which by definition, is 5 amino acids in length, one permutation is to have 3 aromatic residues in one peptide sequence of the pentapeptide library at positions 1, 2, 3 of the 5 positions of the pentapeptide. Another permutation would be 1, 2, 4. The rest of the permutations for 3 aromatic residues are: 1, 2, 5; 1, 3, 4; 1, 3, 5; 1, 4, 5; 2, 3, 4; 2, 3, 5; 2, 4, 5; and 3, 4, 5. So there are a total of 10 permutations for 3 aromatic residues in a pentapeptide library constructed as described in the specification.

For a pentapeptide having 4 aromatic residues, the permutations are: 1, 2, 3, 4; 1, 2, 3, 5; 1, 2, 4, 5; 1, 3, 4, 5; and 2, 3, 4, 5. So there are 5 permutations for 4 aromatic residues in a peptapeptide library constructed as described in the specification.

For a pentapeptide containing 5 aromatic residues, there is one permutation: 1, 2, 3, 4, 5. Thus, all peptides in the pentapeptide library containing 5 aromatic residues have either D-phenylalanine, D-tyrosine or D-tryptophan at each of the 5 positions in the sequences.

For each position that has an aromatic residue, that residue can be one of the 3 aromatics specified. So, for the permutation of positions 1, 2, 3, each containing one of the 3 aromatics, and in the pentapeptide library, there are 3 to the 3rd power number of peptides = 27. The other 2 positions, i.e., positions 4 and 5 have either D-alanine or glycine. So the number of pentapeptides having 3 aromatics at positions 1, 2, 3, also can have 2 to the 2nd power = 4 of possible sequences for those pentapeptides containing 3 aromatics at positions 1, 2, 3 and either D-alanine or glycine at positions 4 and 5. So there are now 27 x 4 = 108 different peptide sequences that contain 3 aromatic residues at positions 1, 2, 3 in the pentapeptide library. Since there are 10 permutations for positions of any 3 of the aromatics in the 5 positions of the pentapeptides in the library, there are a total of 10 x 108 = 1080 peptides in the pentapeptide library that contain 3 aromatic residues.

For the pentapeptides containing 4 aromatic residues, there will 3 to the 4th power (i.e., 4 positions) = 81 x 2 (D-alanine or glycine at the other position) for each permutation. Five (5) permutations x 162 = 810 sequences of the pentapeptide library will have 4 aromatic residues.

For the pentapeptides that contain 5 aromatic residues, i.e., an aromatic residue at each position, there are 3 to the 5th power = 243 different sequences in the pentapeptide library so the total number of peptides containing 3 or more aromatic residues is 1080 plus 810 plus 243 = 2133; divide that number by the total number of pentapeptide sequences in that library (3125); 2133 divided by 3125 = 0.68256 = 68.256% (at least 68%).

The percents of peptides, containing whatever residues one wishes to specify, in a combinatorial library made as described in the specification, can be calculated and such percents are intrinsic to the library, and cannot be anything else.

Hexapeptide Combinatorial Library:

The hexapeptide library contains 20 permutations of sequences with 3 aromatics, 15 permutations with 4 aromatic residues, 6 permutations with 5 aromatics, and 1 permutation with 6 aromatic residues; the remaining positions again are occupied by either glycine or D-alanine. So the total number of peptides with 3 or more aromatic residues is 3 to the 3rd power x 2 to the 3rd power x 20 permutations, plus 3 to the 4th power x 2 to the 2nd power x 15 permutations, plus 3 to the 5th power x 2 x 6 permutations, plus 3 to the 6th power x 1 permutation which totals to 12,825 hexapeptides containing 3 or more aromatic D-amino acids. The total number of sequences in the library is 15,675; divided into 12,825 = 0.8208 or 82.08% (at least 68%).

Heptapeptide Combinatorial Library:

There are 35 permutations of sequences with 3 aromatic residues; 30 permutations of sequences with 4 aromatic residues; 20 permutations of sequences containing 5 aromatic residues; 7 permutations of sequences containing 6 aromatic residues; and 1 permutation for positions of peptide that contain 7 aromatic residues (all seven positions have 1 of the 3 aromatic D-amino acids); other non-aromatic positions occupied by either glycine or D-alanine. The total number of peptides containing 3 or more aromatic residues is then: 3 to the 3rd power x 2 to the 4th power x 35 permutations, plus 3 to the 4th power x 2 to the 3rd power x 30 permutations, plus 3 to the 5th power x 2 to the 2nd power x 20 permutations, plus 3 to the 6th power x 2 x 7 permutations, plus 3 to the 7th power, which adds to 66,393 sequences that contain 3 or more aromatic D-amino acids; there are a total of 78,125 sequences in the library; so the 66,393 sequences is 0.8498 fraction of the total or 84.98% (at least 68%).

Tetrapeptide combinatorial Library:

There are 189 tetrapeptides that contain 3 or more aromatic residues in the library (4 permutations for 3 aromatics and 1 permutation for 4 aromatics: 3 to the 3rd power plus 3 to the 4th power = 189 sequences divided by the total of 256 = 73.8% (at least 68%).

Tripeptide Combinatorial Library:

Because the peptides are only 3 amino acids in length, the library would consist of only the 3 aromatic residues, and thus all tripeptides would contain 3 aromatic residues (100%) (at least 68%).

Responses to the Examiner

On page 3, Response to Arguments, first paragraph, the examiner cites paragraph 0015 of the specification as stating "still more suitably, 40% or even 50% **or more** (emphasis added) of the D-peptides comprise at least three or more aromatic D-amino acid residues. The examiner states: "Notably the above passage recites enrichments of aromatic amino acids outside the range of 68 – 100% (i.e., at least 68%) set forth in claim 5." 50% or more would encompass any percent value above 50%, including the 68% figure. Also in paragraph 0016 that the pentapeptide library is said to contain about 34% of peptides containing 3 aromatic D-amino acids and about 25% of peptides

containing 4 aromatic D-amino acids, which is greater than 50%, and, when the peptides containing 5 aromatic D-amino acids are included adds up to the 68% figure.

V. Claims are Enabled

Claims 5, 44, 46 and 50 were rejected as not enabled.

On page 6 of the examiner's response, last paragraph, section (4) "The level of one or ordinary skill:" the examiner admits that "the level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability,* would have to engage in undue (non-routine) experimentation to carry out the invention as claimed."

We respectfully and most emphatically disagree with the examiner's opinion for the following reasons:

1. The peptide libraries were made by the methods described in 0047, 0048 and 0049 of the specification and a number of commercial firms can synthesize such libraries.

2. Descriptions in sections 0050 through 0053 relate how the screening procedure is performed, and how positive beads are selected and then the peptide sequences of individual beads determined by commercial or academic labs with the equipment to do so.

One of ordinary skill could also certainly count positive beads and calculate percents positive in any experiment as described in sections 0050 through 0070, as well as make tables of sequences found as in 0074 and 0080, in addition to performing binding studies as described in 0082.

A person with knowledge of peptide and protein structure would understand why peptides enriched in the aromatic amino acids would exhibit high affinities and specificities to many proteins of interest. Based on the unusual and little understood ways that the ring structures of aromatic amino acids non-covalently bind to each other, and to other amino acids, and that many protein binding sites contain one or more aromatic amino acid R groups ring structures projecting into their binding sites, it was postulated that short peptides, enriched in the aromatic amino acids, could bind to such sites with high affinities and specificities. It was found indeed that 3 or more aromatic D-amino acids could bind proteins with high affinities and specificity.

Furthermore, it was shown and disclosed that the claimed library was useful in binding molecules of interest: as described in sections 0027 through 0035; and as in table 6 of section 0074 and table 7 of 0080 which shows that many peptides were identified as binding proteins of medical interest; sections 0086 through 0096 showed an application of such peptides. Also the inventor had

possession of the claimed invention as demonstrated at least in the following sites in the specification:

> [0029] ... Preliminary data using live mice suggest that the D-peptides reduce toxicity of the BNT/A toxin in mammals.
>
> [0034] In other Examples, antibodies were screened for the ability to bind to D-peptides in the D-peptide library...

(see Table 6, [0082] Sequences of D-peptides binding to tested lectins or toxins.)

VI. Solubility

Claim 5 is amended to read: "so that the linked D-peptides are accessible for binding with proteins in a water based fluid phase added to the support." This amendment will also take care of the examiner's concern about the "antecedent basis problem in claim 44."

Amended claim 5 relates that the peptides of the present application are able to interact with other molecules in a water based solution, e.g., bind to proteins.

As exemplified in the specification, peptides on supports can also be functionally soluble:

> [0019] Because the polyoxyethylene arms of the TentaGel beads are water soluble, the conformations of the D-peptides are determined primarily by thermodynamics and by their primary sequence. As one skilled in the art will appreciate, the D-peptide may be attached to any suitable support. For example, D-peptides comprising at least one lysine residue at the carboxy terminus were synthesized and covalently coupled to maleic anhydride-coated 96-well polystyrene plates for use in binding assays. The D-peptides thus coupled to the polystyrene plates have free amino termini.
>
> [0037] For those D-peptides of the present invention intended for administration to a mammal, (e.g., a mammal exposed to a toxin), the D-peptides are suitably constructed or modified so as to enhance solubility. In the Examples below, D-peptides administered to mice were designed and synthesized to include three D-lysine residues at the C-terminal ends of the D-peptides to enhance solubility. It is envisioned that from one to four D-lysine residues at the C-terminus would enhance solubility. It is further envisioned that any amino acid residue tending to promote solubility could be included at the C-terminus, including R, D and/or E amino acids. It is yet further envisioned that the D-peptides could be derivatized at the C-terminus with substituents other than amino acids to promote solubility. Such substituents may include a polyoxyethlene polymer or a compound containing multiple hydroxyl groups, such as monosaccharide or polysaccharide. It is also envisioned that one or more of the D-peptides

> may be chemically coupled to a water soluble compound such as a polysaccharide or protein to promote solubility in water-based solvents or physiologic fluids. It is envisioned that the D-peptides could be physically incorporated into or chemically coupled to structures such as liposomes in order to promote solubility in water-based physiologic fluids. It is further envisioned that more than one D-peptide could be coupled to a carrier molecule so as to multimerize the resulting conjugated compound for administration to a mammal with the potential effect of achieving a functional affinity (avidity) of the D-peptide multimer. It is yet further envisioned that more than one D-peptide identified as binding to a protein of interest may be coupled to a carrier compound to potentially achieve functional affinity effects. Additionally, it is envisioned that one or more of the D-peptides may be conjugated to another peptide, protein or carbohydrate sequence (for example, the sialyl-lactose carbohydrate sequence known to have a binding site on the botulinum neurotoxin) in order to enhance binding of such conjugates to a protein of interest.
>
> [00043]...carrier compositions can include...water soluble compositions, such as liposomes, microsponges, microspheres, microcapsules, aqueous base ointments, water-in-oil or oil-in-water emulsions or gels.

The examiner cites to a publication by Merrifield for support of his perception that the claimed peptide library cannot be soluble. In Merrifield's method, the growing peptide chain necessarily must be accessible, solvated, in the fluid phase in order for the next amino acid derivative to achieve a covalent bond via the catalyst used. If the end amino acid of the growing peptide chain were not solvated and accessible, no chemical reaction would occur.

These issues are discussed extensively in the specification in sections 0019, 0037 and 0043.

The paper by Merrifield referred to on page 7 of the Office Action states that the solid particles to which the growing peptide chains are attached is insoluble - not the peptide chain itself. And although the Merrifield report is a method, it is not the only method of peptide synthesis. Furthermore, Merrifield indicates that the advantage of his system might be for "higher molecular weight polypeptides" (p. 2149).

The peptide chain needs to be "soluble" in the solution to which the protected amino acids are added for the next addition or reaction would not occur, i.e, the peptide chain needs to be accessible to the protected amino acid derivative added for the next adition of such amino acid . The great advantage of the Merrifield system is the reaction components, the protected amino acid derivative and the catalyst plus solvent, can readily be separated from the growing peptide chain on

the beads simply by washing the beads with solvent only. The second advantage of the Merrifield system is that certain protected amino acids do not couple with sufficient yields to assure complete reaction at that position; the Merrifield system allows either use of high molar ratios of the protected amino acid compared to the effective concentration of the peptide chain on the beads, and/or adding the same protected amino acid a second time to insure complete addition. Thus, the resultant peptide product is more likely to be nearly 100% of the sequence desired. And although the Merrifield report is a method, it is not the only method of peptide synthesis, i.e., in certain circumstances a solution phase synthesis, or certain step in synthesis, is desired or necessary. Furthermore, Merrifield indicates that the advantage of his system might be for "higher molecular weight polypeptides" (p. 2149) (this statement indicates that for higher MW peptides, the incomplete addition of amino acids, as would occur in solution phase syntheses, would result in a more complex mixture of peptides of incomplete additions of amino acids at all and certain positions.

The system as described by Merrifield is comparable in characteristics to that described in the present specification. The growing peptide chain as used in Merrifield needs to be solvated on the beads, i.e., solvated in the solvent used, in order for the chemical reaction of another amino acid protected derivative to covalently bond to the peptide chain. In the present system, the aromatic peptides need to be solvated in the water based solvent in which the protein is added, and be therefore accessible for the protein in the water based solvent to non-covalently bind to the protein binding site(s). Anyone of ordinary skill in the art (field) would understand this. A Declaration from an expert can be obtained if necessary for allowance.

To explain further, with support from the specification, when peptides are delivered *in vivo* their solubility can be enhanced by e.g., adding 3-4 lysines to the C-terminal end [0088].

VII. Other Issues

The examiner suggested "possible insertion of D- before aromatic in claim 5, line 4." The "D-" is now placed there.

Claim 50 is amended so the arguments on pages 3-5 are moot. These pages mostly just repeat well known sections from MPEP. It should however be noted for the record that D-isomers of non-naturally occurring amino acids are in the specification at par 0022 and 0025.

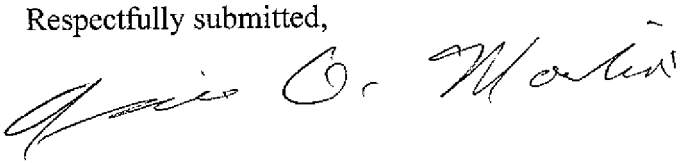
Applicant questions the interpretation in the Interview Summary of April 1, 2009, "plurality means most frequent." Applicant interprets "plurality" as "more than one." The examiner, in his

Substance of the Interview---, "interprets that "consisting of a plurality" as still being open to other peptides (e.g., L-peptides)." This comment by the examiner is incomprehensible since claim 5 states "a plurality of D-peptides" and the configurational designation of "D" occurs 6 more times in the claim. Furthermore, claim 46 states that the aromatic residues "are selected from a group consisting of D-tryptophan, D-tyrosine, and D-phenylalanine." How can it be made more clear that the claim specifies D-configuration amino acids.

VIII. Conclusion and Summary

Applicant thanks the examiner for withdrawing previous rejections, and requests allowance of the pending claims. If necessary, another interview is requested. Please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (45240-105719).

Respectfully submitted,



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